Exhibit A

HARRISON'S

PRINCIPLES OF INTERNAL MEDICINE

TWELFTH EDITION

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Twelfth Edition

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represe[illegible] modified pathologic product[illegible]

Six[illegible] CJD demonstrate an autoim[illegible] antibody against 14-3-3 neurofilaments. The antibody usually appears late in the disease. It can occasionally be found in normal subjects. The significance of this antibody is unclear.

CJD may be mistaken for Alzheimer's disease with myoclonus. In this situation, the presence of cerebellar signs provides strong evidence against the possibility of Alzheimer's disease. At times, CJD can be confused with multi-infarct dementia, alcoholic or nutritional deficiency syndromes, or primary brain tumors. The hallmarks of the disorder (mental deterioration, multisystem neurologic signs, myoclonus, and typical EEG changes) evolving over a period of months in a middle-aged patient usually secures the diagnosis.

The CJD agent has been found in lymph nodes, liver, kidney, spleen, lung, cornea, and CSF of patients with the disorder. The way the disease is acquired naturally is unknown. Incubation periods as long as 20 years may occur in natural transmission. The higher incidence of CJD among Israelis of Libyan origin who eat sheep's eyeballs has led to speculation that the disease may be naturally transmitted by the ingestion of scrapie-infected meat. There is an unexpectedly high incidence of previous brain or eye operations among CJD patients. Human-to-human transmission has occurred by corneal transplantation, by the implantation of contaminated stereotactic electroencephalographic electrodes, by cadaveric dura mater graft, and by the parenteral administration of growth hormone prepared from cadaveric human pituitary glands. Transmission of CJD has not been linked to blood transfusion.

There is no evidence of an increased risk among spouses, friends, and medical or nursing personnel caring for CJD patients. The patient's CSF and blood should be considered, however, as potential sources of infection. Precautions should be taken to avoid autoinoculation with needles, scalpels, or other instruments that have been contaminated by the patient's tissues. Maximum care should be taken to avoid accidental percutaneous exposure to blood, CSF, or tissue. Contaminated skin can be disinfected by a 5- to 10-min exposure to 1 *N* sodium hydroxide followed by extensive washing with water. Contaminated material should be steam-autoclaved for 1 h at a temperature of at least 132°C or immersed for 1 h in 1 *N* sodium hydroxide or a 10% sodium hypochlorite solution. More detailed guidelines for the handling of materials from patients with these disorders have been developed by the Centers for Disease Control. These should be applied to all patients who have evidence of rapid intellectual deterioration, particularly when it is associated with myoclonus.

There is no effective treatment for CJD. Claims that amantadine hydrochloride is effective have not been substantiated.

GERSTMANN-STRÄUSSLER-SCHEINKER (GSS) DISEASE

GSS disease is an inherited autosomal dominant illness characterized by spinocerebellar ataxia with dementia and plaquelike deposits of amyloid in the brain. Inoculation of brain tissue from GSS disease produces spongiform encephalopathy in nonhuman primates. PrP and PrP-immunoreactive amyloid plaques accumulate in the brains of these patients. The putative gene for the syndrome is linked to the PrP gene, codon 102, on the short arm of chromosome 20. A substitution of leucine for proline at this codon may lead to the development of the GSS disease. The usual onset of the disease is in the fifth decade. GSS disease follows a lengthy course, usually on the order of 2 to 10 years. Ataxia is prominent in the early phase of the illness; dementia follows later. The patient's symptoms and signs are reminiscent of olivopontocerebellar atrophy. Pathologic changes include spinocerebellar and corticospinal tract degeneration, extensive [illegible] degeneration. Like other human [illegible] rologic disease and spongiform changes in chimpanzees. Numerous other transmission attempts from patients with both familial and nonfamilial Alzheimer's disease have been negative. At present, there is no direct evidence to indicate that Alzheimer's disease is caused by a slow virus.

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356 DEMYELINATING DISEASES

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The demyelinating diseases comprise a group of neurologic disorders important both because of the frequency with which they occur and the disability that they cause. Demyelinating diseases have in common the pathologic feature of focal or patchy destruction of myelin sheaths in the central nervous system accompanied by an inflammatory response. Some degree of axonal damage may occur as well, but demyelination always predominates. Multiple sclerosis is the most common of the demyelinating diseases. Its cause is not known. Current opinion holds that autoimmunity, perhaps induced by viral infection, is likely to be implicated in its pathogenesis. Acute disseminated encephalomyelitis and its hyperacute variant, acute hemorrhagic leukoencephalitis, are acute and monophasic immune-mediated demyelinating diseases. HTLV-I–associated myelopathy provides an example of a virus-initiated chronic demyelinating disease.

Myelin loss occurs in other conditions as well, but in these others an inflammatory response is lacking. Included are genetically determined defects in myelin metabolism, exposure to toxins such as carbon monoxide, and opportunistic viral infection of oligodendroglia (progressive multifocal leukoencephalopathy) against a

MULTIPLE SCLEROSIS

This disease usually presents in the form of recurrent attacks of focal or multifocal neurologic dysfunction, reflecting lesions within the central nervous system (CNS). Attacks occur, remit, and recur, seemingly randomly over many years. The disease begins most commonly in early adult life. The frequency of flare-ups is greatest during the first 3 to 4 years of disease, but a first attack, which may have been so mild as to escape medical attention and can barely be recalled, may not be followed by another attack for 10 to 20 years. During typical episodes, symptoms worsen over a period of a few days to 2 to 3 weeks and then remit. Recovery is usually rapid over a period of weeks, although at times it may extend over several months. The extent of recovery varies markedly between patients and from one attack to the next in the same person. Remission may be complete, particularly after early attacks; often, however, remission is incomplete and as one attack follows another, a stepwise downward progression ensues with increasing permanent deficit.

In perhaps as many as one-third of cases the disease declares itself as a slowly but inexorably progressive illness. This is particularly likely to be the case if onset is after age 40. Although occasional patients die within the first few years of disease onset, most do not, and the average survival from multiple sclerosis (MS) is better than 30 years after onset of disease.

Multiple sclerosis is pleomorphic in its presentations. The clinical picture is determined by the location of foci of demyelination within the CNS. Classic features include impaired vision, nystagmus, dysarthria, decreased perception of vibration and position sense, ataxia and intention tremor, weakness or paralysis of one or more limbs, spasticity, and bladder problems.

Criteria which must be satisfied to establish a diagnosis of clinically definite MS include a reliable history of at least two episodes of neurologic deficit and objective clinical signs of lesions at more than one site within the CNS. Demonstration of additional lesions by laboratory tests [e.g., evoked potentials, urologic studies, computed tomography, or, most sensitively, magnetic resonance imaging (MRI)], in concert with one objective clinical lesion, also fulfills the criteria. A finding of increased cerebrospinal fluid immunoglobulin with oligoclonal bands supports the diagnosis but will not substitute for the above criteria. Clinically probable MS is defined as either two attacks with clinical evidence of one lesion or one attack with clinical evidence of two lesions (or one clinical and one paraclinical lesion). Follow-up studies of probable MS patients indicate considerable diagnostic imprecision in this category. When signs pointing to damage of white matter tracts in optic nerves, brainstem, and spinal cord are present together and more than one attack is known to have occurred, a diagnosis of multiple sclerosis can be made with greater than 95 percent certainty. In the early years of the disease, when few exacerbations have occurred and fixed deficits are mild, the diagnosis may be very difficult, and single or multiple focal lesions due to other diseases must be excluded.

PATHOLOGY Many scattered, discrete areas of demyelination, termed *plaques*, are the pathologic hallmark of multiple sclerosis. Macroscopically, plaques appear as gray-pink sharply defined areas which stand out against the surrounding white matter of the central nervous system. Lesions may extend into gray matter, although nerve cell bodies are seen to be preserved on microscopic examination. Plaques vary in size from a few millimeters to several centimeters; larger ones form by coalescence of smaller ones and by expansion of their margins. Plaques may be found anywhere in the white matter but typically occur in the paraventricular areas of the cerebrum and cerebellum, and within the brainstem and spinal cord. Their topography corresponds to that of the venous drainage of the brain and spinal cord, but no particular anatomic structures are respected. The peripheral nervous system is not affected. The number of plaques found at autopsy invariably exceeds the number expected on the basis of clinical signs. Many plaques, therefore, are clinically silent; this underlines that substantial impulse conduction occurs across regions of demyelination. In fact, autopsy studies indicate that 20 percent of multiple sclerosis cases are clinically silent during life.

The microscopic features of multiple sclerosis lesions depend on their age. Typically, lesions of different ages and evidence of new activity about the margins of old lesions are encountered. Active multiple sclerosis lesions feature T-lymphocyte and monocyte-macrophage accumulations about venules and at plaque margins where myelin is being destroyed. The inflammatory cells that invade the white matter and the soluble mediators that they release (lymphokines and monokines) are held responsible for the myelin breakdown. Macrophages also function as scavengers of myelin debris; fat-laden macrophages may persist for months, perhaps for years, after the acute inflammatory response has subsided. Plasma cells accumulate within plaques and are usually found at or near their centers.

An astroglial response at or just beyond the margins of actively demyelinating lesions is characteristic. In established, inactive plaques, a thick mat of fibrillary gliosis throughout the demyelinated regions is usual, and only a few residual perivascular macrophages are found. Oligodendrocyte number has been said to be normal or increased at the plaque margin. Yet, oligodendrocyte number is reduced within plaques, indicating that ultimately, this cell type is lost in multiple sclerosis. Indeed, damage to oligodendrocytes may be the primary event.

Only limited regeneration of myelin occurs in multiple sclerosis (shadow plaques). Absent remyelination, mechanisms responsible for recovery from an MS attack along segmentally demyelinated axons are likely multiple. Resolution of edema, as documented by MRI or CT scan, may permit return of saltatory conduction along segmentally demyelinated axons. Restoration of conduction may also relate, in part, to insertion of K^+ channels along the length of demuded axonal segments rather than exclusively at the nodes of Ranvier as is the situation in myelinated nerve.

Axons within plaques tend to be spared, although in acute lesions frank necrosis with loss of axons sometimes occurs. At least 10 percent of multiple sclerosis plaques show marked axonal loss, and ultrastructural studies indicate that loss of axons may be more general than can be appreciated by routine histology. All gradations of pathologic change between the extremes described above are encountered.

The pathologic features of MS fail to account for the hour-to-hour and day-to-day waxings and wanings in function so characteristic of the disease. Conduction of impulses through demyelinated nerve is compromised and is further altered by transient changes in the internal milieu such as alterations in temperature and in electrolyte balance or by stress. Fever, or even minor increases in body temperature, such as may follow a hot bath or exercise, may cause a failure of conduction through demyelinated regions and lead to evanescent symptoms and signs. The mechanism of this axonal fatigability is unknown, but some type of conduction block is assumed to occur. It is important to distinguish transient fluctuations in symptomatology of the type just described from attacks of disease.

ETIOLOGY The cause or causes of MS remain unknown. A role for immune-mediated or infectious factors has been proposed, but data to support these postulates are fragmentary and indirect. Isolation of HTLV-I–related viral components from CNS tissue in patients with MS is reported, but the etiologic significance of these findings remains uncertain (see Waksman).

Epidemiology Epidemiologic studies have established several facts which will ultimately have to be incorporated into any coherent theory of the disease. Average age of onset of the first clinical episode of MS falls within the third and fourth decades. Females account for 60 percent of cases. For disease to begin in childhood or beyond the sixth decade is uncommon but not unknown.

In general, incidence in temperate climatic zones exceeds that in tropical zones; but variations within regions with similar climates do exist; hence the effect is not simply one of latitude or temperature. The incidence of MS in northern Europe, Canada, and the northern United States is approximately 10 new cases each year per 100,000

persons between the ages of 20 and 50. [illegible] lia, New Zealand, and the southern United St[illegible]s one-third to one-half of that; in Japan, elsewhere in the Orient, and in Africa MS is rare. Some epidemiologic evidence also suggests that persons migrating from high- to low-risk regions as children may be partially protected from MS. The data are consistent with the existence of an environmental factor, possibly a virus, and perhaps geographically restricted, that influences development of MS.

Genetic factors The incidence of MS among American Indians and blacks is lower than that among whites living in the same regions. This suggests that genetic factors also influence disease susceptibility. Blood relatives of MS patients (children, siblings) have an at least fifteenfold increased risk of developing MS. This could reflect an interplay of several genetic factors, shared exposure to an environmental factor, or a combination of the two. Concordance for MS between identical twins (25 percent) is markedly greater than for fraternal twins (2 to 3 percent). Family studies have failed to reveal any predictable genetic pattern but do argue persuasively for a genetically determined predisposition to disease.

Certain histocompatibility antigens (HLA) are overrepresented in patients with MS. Among whites with the disease the HLA-B7, -DR2, and -DQW1 alleles occur with increased frequency. Most illnesses with which an HLA association has been shown are autoimmune or infections in nature, a finding in keeping with current thought about the etiology of MS. Many American blacks with MS express the DW2 allele; this allele is rare in blacks in Africa, among whom MS is virtually unknown. It follows that an HLA-linked genetic factor which predisposes to MS exists, but inasmuch as the vast majority of persons bearing DR2 or DQW1 do not develop the disease, additional genetic or environmental factors must play a role. Paradoxically, siblings concordant for MS have concordance rates for HLA haplotypes little above those expected by chance. The HLA-B12 allele is less frequent in MS than in the population at large. This finding suggests that genetically determined protective factors may operate in MS.

Autoimmune factors The lesions of MS are mimicked by those of experimental allergic encephalomyelitis (EAE), an autoimmune disease induced in animals by immunization with myelin. Lesions of EAE are demyelinating, perivenular, plaque-like, occur in chronic and recrudescent forms, and have an inflammatory infiltrate composed of lymphocytes, macrophages, and plasma cells. T lymphocytes sensitized to specific myelin antigens (myelin basic protein or proteolipid protein) can adoptively transfer the disease. In MS, sensitivity to these myelin antigens cannot be demonstrated. Chronic demyelination can be a consequence of viral infection in animals. Demyelination follows infection of mice with Theiler's murine encephalomyelitis virus; infected animals do not exhibit sensitivity to myelin antigens. Attempts to find any antigen to which only MS patients react have failed.

Attacks of MS are associated with changes in peripheral blood monocyte and lymphocyte properties. Reported changes include heightened prostaglandin secretion by macrophages (which may in turn influence lymphocyte properties), reduced suppressor cell function, an increased number of activated T cells as evidenced by their expression of certain surface antigens, heightened T-cell–dependent in vitro immunoglobulin secretion, deficient interferon secretion, and possibly reduced natural killer (NK) cell function. Whether these changes relate to the etiology of MS is not known.

Within the cerebrospinal fluid (CSF), T-cell activation is apparent during active disease. Excessive IgG production within the CNS is characteristic of MS at all stages of disease; whether this reflects the presence of some stimulator of B cells in the brain in MS or is the result of a defect in immune regulation is not known. Viral infection of brain remains a possible cause of MS, despite the fact that all attempts to isolate, rescue, or "passage" a virus from MS brains or to visualize a virus within them have failed.

Precipitating factors Most attacks of MS occur without any evident antecedent. There is a modestly increased risk for an attack following viral infection. Injury and [illegible]otion[illegible]ts have been claimed to precip[illegible] attacks of MS; evidence in support of these claims remains anecdotal and nonpersuasive. The probability that an attack of MS will occur during the first 6 months after pregnancy is greater than chance would predict, but this observation is counterbalanced by a decreased risk of an attack during the second and third trimesters of pregnancy. In established cases, trauma, including lumbar puncture, myelography, and surgery, has not been shown to relate to attacks or to progression of disability nor has emotional turmoil been shown to alter the tempo at which the disease evolves. Experience has also shown that vaccinations do not provoke attacks of MS.

CLINICAL MANIFESTATIONS The first attack of MS may declare itself as a single symptom or sign (45 percent) or as more than one (55 percent). Approximately 40 percent of MS patients will have an episode of optic neuritis, either as their first difficulty or at some point along the course of their disease. Optic neuritis presents as loss of vision, partial or total, usually in one eye, seldom in both, and is often associated with pain on movement of the eye. Macular vision tends to be most affected (central scotoma), but a wide range of field defects may occur. Disturbances of color perception sometimes provide an early indication of mild disease. Fewer than half of optic neuritis patients will show evidence of an inflamed optic nerve head (papillitis); most show no changes in the optic disc at the outset, indicating that the demyelinating lesion is developing some distance behind the nerve head (retrobulbar neuritis). Both forms of optic neuritis will be followed by optic nerve atrophy, detected as pallor of the optic disc.

It is important to recognize that cases of optic neuritis occur as an isolated event. Nonetheless, 35 percent of men and 75 percent of women with optic neuritis go on to develop MS in the ensuing 15 years. Unfortunately, it is difficult to predict who will and who will not develop the disease, although presence of oligoclonal bands in the CSF and of multifocal cerebral lesions on MRI scanning are seemingly unfavorable findings. Whether optic neuritis occurring alone and for unknown reasons constitutes a *forme fruste* of MS with but a single attack is not known. Approximately one-third of patients with optic neuritis recover completely, one-third partially, and one-third little or not at all. Visual evoked response testing reveals prolonged latencies of the evoked potentials in more than 80 percent of established cases of MS; less than half of these can describe an antecedent optic neuritis. Clearly subclinical involvement of the optic pathways is common.

Symptoms and signs of neurologic dysfunction arising from brainstem, cerebellar, and spinal cord lesions are frequent in MS. Diplopia may occur either because the third, fourth, or sixth cranial nerve pathways are damaged along their course within the CNS or because an internuclear ophthalmoplegia (INO) has developed (see Chap. 23). An INO reflects involvement of the medial longitudinal fasciculus. The sign consists of an inability to adduct one eye on attempted lateral gaze together with full abduction of the other eye, which shows horizontal nystagmus. Bilateral INO in a young adult is virtually diagnostic of MS, although a few instances of bilateral INO in systemic lupus erythematosus are on record. Another clinical feature of brainstem involvement is either facial hypesthesia or tic douloureux (fifth cranial nerve). When tic douloureux occurs in a young adult, the possibility of underlying MS should be seriously entertained. Bell's palsy or hemifacial spasm (seventh cranial nerve), vertigo, vomiting, and nystagmus (vestibular connections of the eighth cranial nerve) are also frequent; less commonly there is complaint of deafness. Involvement of cerebellar connections results in ataxia which can affect speech (scanning), head or trunk (titubation), limbs (intention tremor), and stance and gait. Cerebellar ataxia may be combined with sensory ataxia due to involvement of the spinal cord.

Spinal cord lesions produce a myriad of motor and sensory problems. Corticospinal tract interruption results in the classical features of upper motor neuron dysfunction (weakness, spasticity,

hyperreflexia, clonus, Babinski response, loss of abdominal skin reflexes). Posterior column lesions cause loss, or diminution, of joint-position and vibration senses as well as the frequently encountered complaints of tingling or tightness of the extremities and of bandlike sensations about the trunk. Less often pain and temperature sensations are lost or diminished, reflecting spinothalamic tract involvement. Partial lesions of sensory tracts or of the root entry zones of sensory nerves can produce painful dysesthesias as well as interruption of reflex arcs. On occasion, spinal cord lesions will result in paroxysmal symptoms including tonic spasms which can be painful.

Symptoms of bladder dysfunction, including hesitancy, urgency, frequency, and incontinence, are common features of spinal cord involvement. Equally common is bowel dysfunction, particularly constipation. Males with MS, if questioned, often complain of sexual impotence; methods exist to distinguish physical from psychogenic causes. Patients with MS may experience an electric shock-like sensation on flexion of the neck, called Lhermitte's sign.

Severe spinal cord lesions can result in loss of function, sometimes total, below the level of the lesion; less complete lesions can result in the hemicord syndrome of Brown-Séquard (see Chap. 361). When either of these events occurs, it is referred to as a transverse myelitis. A single episode of transverse myelitis not followed by subsequent progression of disease may, as with an isolated episode of optic neuritis, represent a *forme fruste* of MS, although less than 10 percent of acute transverse myelitis cases develop MS. Again as with optic neuritis, approximately one-third of patients with transverse myelitis recover completely, one-third partially, and one-third not at all. Spinal cord involvement is the predominating feature in most advanced cases of MS.

Cerebral symptoms may occur in MS due to extensive involvement of subcortical and central white matter. With extensive lesions of brain, intellect may suffer, sometimes disastrously. By far the most frequent emotional feature of MS is depression. Euphoria, when it occurs, indicates widespread cerebral disease and is often associated with dementia and pseudobulbar palsy. Three to five percent of patients (twice the expected rate) will have one or more epileptic seizures, presumably because of extension of plaques into gray matter. Focal neurologic signs of cerebral origin, such as hemiparesis, homonymous hemianopsia, and dysphasia, while seen in MS, are rare.

Neuromyelitis optica and MS An ill-defined symptom complex known as Devic's syndrome, or neuromyelitis optica, is considered by some to be an entity distinguishable from MS. The complex is characterized by acute optic neuritis, usually bilateral, which is followed, or less frequently preceded, within hours to weeks by transverse myelitis. The cerebrospinal fluid (CSF) may show a pleocytosis with polymorphonuclear cells and a protein content that is higher than is usual for MS. Pathologic examination in fatal cases reveals more tissue destruction and cavitation than is expected in MS, although this may bespeak no more than the intensity of the process.

COURSE OF ILLNESS AND PROGNOSIS The clinical course of MS is unpredictable. In general, symptoms which appear acutely and those referable to sensory paths and the cranial nerves have a more favorable prognosis than those developing insidiously or involving motor and especially cerebellar function. According to McAlpine, 80 percent of patients who have a purely exacerbating and remitting disease have unrestricted function after 10 years. Of cases in which exacerbations and remissions are superimposed on a progressive tempo of evolution, 50 percent are disabled after 10 years. In cases that have a purely progressive course from the outset (in these the brunt of the disease usually falls on the spinal cord) the long-term prognosis for ambulation is poor.

Rarely MS may be fulminant and fatal within weeks to months. Such cases, which are referred to as acute MS, show intense inflammatory responses within the plaques. Onset in such patients may be with headache, vomiting, delirium, convulsions, even coma, and an array of signs indicating severe compromise of cortical, brainstem, optic nerve, and spinal cord function. Distinction from acute disseminated encephalomyelitis may be difficult in life; at autopsy the lesions are larger and more like those of MS.

DIFFERENTIAL DIAGNOSIS The diagnosis of MS becomes secure when signs referable to multiple lesions of CNS white matter have developed and remitted at different times. Particularly in the early phases of disease, the neurologic symptoms may suggest discrete dysfunction of the nervous system, and other causes of focal disease must be excluded. An excellent clinical rule is that MS should not be diagnosed when all the patient's symptoms and signs can be explained by a single lesion. A common aphorism is that MS presents with symptoms in one leg and signs in both.

Conditions to be excluded vary depending on the sites of the lesions. Abrupt monocular loss of vision may result from impaired vascular supply to the optic nerve, including embolic and thrombotic occlusion of the carotid, ophthalmic, or central retinal arteries; or as an accompaniment of migraine. When monocular visual loss is more gradual, compressive lesions affecting the optic nerve or an optic nerve glioma need to be considered.

In patients presenting with acute or progressive spinal cord disease, the presence of focal lesions affecting the cord and of degenerative-nutritional diseases which selectively affect spinal cord tracts should be considered (see Chaps. 357 and 361). Patients with progressive spastic paraplegia should be evaluated for the presence of intrathecal or extradural neoplasm, vascular malformations, and for cervical spondylosis. Such evaluation often requires a CT body scan, MRI, or myelography. Hereditary ataxias can present as degeneration of multiple CNS tracts, with or without involvement of the peripheral nervous system. Degeneration of posterior columns and corticospinal and spinocerebellar tracts is common in these disorders. Hereditary ataxias are slowly progressive and feature stereotyped symmetric involvement as well as a family history consistent with autosomal dominant, or recessive, inheritance. Amyotrophic lateral sclerosis (ALS) usually presents with prominent lower motor neuron signs (atrophy, weakness, and fasciculations) in addition to pyramidal signs (spasticity, hyperreflexia) and without sensory abnormalities. Subacute combined degeneration of the cord can be excluded by symmetry of spinal symptoms and by a normal serum vitamin B_{12} level, a normal bone marrow, and a normal Schilling test.

When progressive brainstem dysfunction occurs, posterior fossa tumor as well as brainstem encephalitis should be excluded. Single cranial nerve palsies, particularly Bell's palsy, trigeminal sensory neuropathy, or tic douloureux may occur as part of the MS picture, but evidence of multifocal disease must be present before they can be ascribed to MS. When vertigo is the complaint and nystagmus is detected, inner ear disease should be considered as well as the possibility that barbiturates or phenytoin have been taken.

There are several multifocal and recrudescent diseases of the central nervous system which may mimic MS. Systemic lupus erythematosus and other vasculitides may cause scattered and recurring lesions within brain, brainstem, and spinal cord, as can the mitochondrial encephalopathies (MELAS syndrome) (see Chap. 365). Behçet's disease is characterized by recurrent episodes of focal brain disease, CSF pleocytosis, oral and genital ulcers, and uveitis. Other disorders to be excluded include meningovascular syphilis, cryptococcosis, toxoplasmosis, other chronic nervous system infections, and sarcoidosis. Lyme disease can present with focal neurologic signs in the absence of antecedent skin lesions, arthralgias, or peripheral neuropathy (see Chap. 132). HTLV-I–induced disorders are described below. AIDS encephalopathy and myelopathy need also to be considered in progressive cases.

When complaints are vague and findings minimal, a diagnosis of conversion reaction (hysteria) may come to mind. This diagnosis should always be made on the basis of positive criteria for hysteria and never as a "diagnosis by exclusion." Early in its course, MS is mislabeled as hysteria with distressing frequency. Patients with MS may develop superimposed hysterical phenomena adding to the complexity of the clinical syndrome.

A few patients present with pain as their principal symptom. Awareness of its occurrence in MS and careful attention to a thorough examination will usually clarify the diagnosis.

A firm diagnosis of MS should only be made when the evidence is unequivocal. Aside from the distress that such a diagnosis causes, it will serve to explain almost any subsequent neurologic event and may divert attention away from other possibly treatable diseases.

LABORATORY TESTS Although the diagnosis of MS continues to depend on its clinical features, laboratory aids have become increasingly useful as supports for the diagnosis. In the vast majority of patients with MS, one or more tests will be abnormal, although normal results do not rule out the diagnosis.

The CSF in MS patients typically reveals only a slight or no increase in cell number. Ninety percent of patients show fewer than 10 cells per microliter in their CSF; cell counts greater than 50 are rare. The cells in the CSF are predominantly T lymphocytes, although rare plasma cells may be found. Some correlation exists between the extent of pleocytosis and disease activity. Higher cell counts also are more typical in early stages of disease. Evidence that the lymphocytes in the CSF are activated not only during exacerbations of disease but also during seeming remission has been presented; this indicates that disease activity smolders at all times, even though neither the physician nor the patient may be able to detect changes. T-cell lines specifically reactive with various viral and nonviral antigens can be derived from the CSF of MS patients, again suggesting that a heterogeneous immune response is ongoing (see discussion of oligoclonal bands below). The CSF of 90 percent of patients contains less than 60 mg/dL of total protein; protein of greater than 100 mg/dL should raise questions about whether the diagnosis is correct.

The most characteristic CSF finding in MS is an increase in immunoglobulin G (IgG) which contrasts with relatively normal total protein and albumin concentrations. IgG levels are increased in 80 percent of MS patients; the increase is greatest in long-standing cases with severe neurologic deficits. Early in the disease, when the diagnosis is most in doubt, IgG values can be normal. IgG levels do not change in any meaningful way with relapses and remissions. Most of the IgG in the CSF is synthesized within the central nervous system. The increased IgG fraction in the CSF explains the first-zone abnormality of the colloidal gold curve, a test of historical interest.

When the CSF IgG from MS patients is subjected to electrophoresis or isoelectric focusing, it fractionates into a restricted number of bands (termed oligoclonal bands). Oligoclonal banding of IgG has also been found in the CSF in a number of acute and chronic central nervous system infections; in subacute sclerosing panencephalitis cases, these bands have been shown to be antibodies to the infective agent. In MS, the IgG bands have not been shown to be directed against any single viral or intrinsic brain antigen; more likely they represent a heterogeneous group of antibodies directed against many antigens. The number of bands in the CSF is greater in those with longer disease duration. It has also been suggested that high levels of IgG and many oligoclonal bands are associated with a severe course. The overall IgG shows further restrictions in its heterogeneity, with the IgG1 being mainly of the $G1m_1$ allotype. Rare cases of MS without increased CSF IgG synthesis or oligoclonal bands have been documented at autopsy.

Within CSF, myelin debris as well as myelin basic protein fragments appear during attacks of disease. Myelin basic protein levels can be measured by radioimmunoassay; the level seems to reflect the extent of myelin breakdown since levels also increase in other disorders associated with white matter breakdown such as stroke.

Conduction of nerve impulses along axons denuded of their myelin is slowed. Evoked response testing provides a sensitive means to detect slowed conduction of visual, auditory, or somatosensory impulses. Such tests employ repetitive sensory stimuli and utilize computer averaging techniques to record the electric responses evoked during the conduction of these stimuli along visual, auditory, or efferent pathways. In normal subjects, the pattern of the evoked responses and time for conduction are highly predictable. One or more of the evoked response tests will reveal slowing of conduction in 80 percent of MS patients; in 30 to 40 percent of patients, abnormal evoked responses are detected without any clinical symptoms or signs in the involved pathway being apparent. Evoked response testing may confirm the presence of additional sites of disease in suspected cases with only a single clinically detectable lesion (see Chap. 349).

Computed tomography (CT) of the brain may reveal low-density lesions within white matter, usually in a paraventricular or subcortical distribution. Enhancement of lesions following intravenous infusion of iodine with delayed scanning indicates the presence of acute lesions with disruption of the blood-brain barrier. Enhancement may disappear as the clinical symptoms resolve. Cortical atrophy with enlarged ventricles is also found in some patients. The incidence of such abnormalities discovered by CT scanning is approximately 25 percent.

MRI is the most sensitive means of detecting lesions of MS. More than 90 percent of patients with clinically definite MS show multifocal cerebral white matter lesions on MRI, better seen with spin-echo (T2-weighted) than with inversion recovery (T1-weighted) images. Serial MRI studies of MS patients with relapsing disease indicate that the frequency of lesion formation, either arising de novo or as an expansion of a preexisting lesion, far exceeds clinical relapse rate. New lesion formation is also observed in progressive MS patients. Lesions typically develop over several weeks and resolve over 2 to 3 months; such resolving lesions likely reflect inflammation and edema rather than demyelination and gliosis. IV administration of gadolinium DTPA can enhance detection of "active" lesions on T1-weighted images (see Chap. 348). MRI lesions suggest that the MS disease process rarely "sleeps." Coalescence of MRI lesions appears to correlate with development of progressive disease. Multifocal cerebral white matter lesions are detected by MRI in 60 to 75 percent of cases of isolated optic neuritis and chronic progressive myelopathy. Technical advances now permit direct detection of inflammatory demyelinating lesions within the optic nerves and spinal cord.

Elevated CSF IgG, abnormal evoked responses, and lesions on CT scans and MRI provide useful adjuncts in evaluation of the patient with suspected MS; however, the clinical findings remain paramount in establishing the diagnosis.

TREATMENT OF MS No effective treatment for MS is known. Therapeutic efforts are directed toward (1) amelioration of the acute episode, (2) prevention of relapses or progression of disease, and (3) relief of symptoms.

In acute flare-ups of disease, glucocorticoid treatment may lessen the severity of symptoms and speed recovery; however, ultimate recovery is not improved by this drug nor is the extent of permanent disability altered. Glucocorticoids likely act chiefly via mechanisms other than modulation of the immune response. They may improve the ability of demyelinated nerve to conduct and reduce edema and inflammation within plaques. Usual regimens utilize either ACTH, to stimulate endogenous glucocorticoid synthesis, or prednisone. ACTH is preferred by many clinicians since the only controlled trials that demonstrated the efficacy of glucocorticoid therapy in flare-ups of MS and in acute optic neuritis were performed with this drug. ACTH is commonly given in a dose of 80 units daily intravenously for 3 to 7 days, followed by intramuscular injections in periodically decreasing doses over the next 2 to 3 weeks. Prednisone, 15 mg qid, is sometimes given rather than ACTH, again, over 3 to 7 days with gradually tapering doses over the next 2 to 3 weeks. Since prednisone is taken by mouth, the treatment is simpler than with ACTH, and an admission to the hospital may sometimes be avoided. Use of long-term daily or alternate-day steroids is not advised.

Immunosuppressive agents such as azathioprine and cyclophosphamide have been claimed to reduce the number of relapses in several series, but there is no consensus about the efficacy of these drugs. Plasma exchange in combination with immunosuppression, total-lymphoid irradiation, cyclosporine A, α-interferon, β-interferon,

or copolymer I remains under active investigation. γ-Interferon provokes exacerbations.

Symptomatic treatment should address both the physical and psychological needs of patients. Patients should avoid excess fatigue and extremes of temperature and eat a balanced diet. Diets containing low levels of saturated fats have been advocated. The use of belladonna alkaloids and bethanechol chloride can help bladder dysfunction. Periodic checks for urinary tract infection should be performed. Bowel training can alleviate disorders of bowel function. Drugs available for the treatment of spasticity include diazepam, baclofen, and dantrolene sodium. Painful dysesthesias, facial twitching, tic douloureux, and tonic spasms may respond to carbamazepine or phenytoin. Occasionally trigeminal root injection is required to relieve tic douloureux (see Chap. 360).

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) may be defined as a monophasic encephalitis or myelitis of abrupt onset characterized by symptoms and signs indicative of damage chiefly of the white matter of the brain or spinal cord. The process may be severe, and even fatal, or mild and evanescent. Pathologic features are those of innumerable minute foci of perivenular lymphocyte and mononuclear cell infiltration with demyelination. The topography of the demyelination corresponds to that of the inflammatory infiltrates. The condition most commonly follows vaccinations against rabies or smallpox or acute infectious illnesses, especially measles, but may occur without any obvious antecedent. The cause is uncertain but is believed by some to represent a hypersensitivity, perhaps to myelin basic protein, and to be the human counterpart of experimentally induced EAE.

ETIOLOGY The entity has been described after two types of vaccination: after rabies vaccination with the Semple vaccine, which contains brain tissue, now seldom used, and after vaccination against smallpox, now seldom performed.

Shortly after introduction of rabies vaccination by Pasteur, it became evident that neuroparalytic accidents could follow this procedure. After a course of injections a sudden encephalitic or myelitic catastrophe might occur coincident with hypersensitivity-type reactions at the sites of vaccine injection. The process clearly involved hypersensitivity to nervous system antigens. The incidence was variously reported as between 1 in 1000 and 1 in 5000 persons vaccinated. An identical syndrome has followed inoculation with noninfected brain material, indicating that killed rabies virus was not the cause; with the introduction of duck embryo killed rabies virus vaccine (which is free of myelinated nervous tissue), the condition has markedly decreased in incidence, although cases continue to be reported from countries where Semple-type vaccines remain in use. Neuroparalytic accidents were most frequent in young adults, the peak age of occurrence corresponding to that of onset of MS. In some cases cellular immune sensitivity to myelin basic protein has been demonstrated.

Smallpox vaccination was also followed by an incidence of ADEM averaging perhaps 1 case per 5000 persons vaccinated but with marked differences between vaccination programs. The complication almost always occurred in conjunction with a primary take rather than a booster-type response. The encephalitis usually followed the peak of the vaccination response by a few days to a week or more but on occasion preceded it. The complication was unknown in children less than 2 years of age; in infants, smallpox vaccination was sometimes associated with an encephalopathy with brain swelling, i.e., toxic encephalopathy.

One case of measles in 1000 is followed by neurologic complications, which are often severe. The mortality rate averages 20 percent, and half the survivors are left with residual damage. The syndrome usually follows the rash by a few days. It bears no relationship to the severity of measles itself. Systemic lymphocyte sensitivity to myelin basic protein has been demonstrated in some patients. All attempts to isolate a virus have failed. Abnormal CSF and changes in the electroencephalogram are observed in perhaps half the children who contract measles, suggesting that subclinical neurologic involvement may be much more widespread than is usually appreciated. A subtle decline in performance and changes in behavior following measles may reflect this inapparent nervous system involvement. Measles vaccination has drastically reduced the frequency of this complication.

An identical clinical picture was seen formerly as a complication of smallpox and is still encountered during or following chickenpox and extremely rarely as a complication of rubella. Demyelinating encephalomyelitis is very rare in mumps; instead there is often a true viral meningitis. A clinical picture identical to postinfectious encephalomyelitis has been described after mycoplasma infections. Despite its striking association with measles, the occurrence of the same clinical picture after several different infections fits better with the postulate that the basic process involves hypersensitivity rather than a direct viral infection of the brain and spinal cord.

CLINICAL MANIFESTATIONS The disease usually begins abruptly. Headache and delirium may give way to lethargy and coma. Coma has an ominous prognosis. Seizures at the onset or shortly thereafter are not infrequent. There may be stiffness of the neck, other signs of meningeal irritation, and fever. Focal signs may be engrafted on this picture, and spinal cord involvement with flaccid paralysis of all four limbs is particularly common. Monoparesis and hemiplegia are also seen. Tendon reflexes may be lost initially only to become hyperactive later; extensor plantar responses are the rule, and sphincter control is generally lost. Sensory loss is variable but may be extensive and severe. Brainstem involvement may be reflected by nystagmus, ocular palsies, and pupillary changes. Some cases may present as a purely spinal cord syndrome and in mild instances with minor signs such as a facial palsy. Chorea and athetosis are rare. Cerebellar signs may predominate, particularly in cases associated with chickenpox. Involvement of motor and sensory peripheral nerves can be documented clinically and electromyographically in some patients. The CSF almost always shows an increase in protein (50 to 100 mg/dL) and lymphocytes (10 to several hundred cells); rarely it is normal. The mortality is 20 percent, and perhaps half the survivors have residual deficits. Recurrences are almost unknown.

The diagnosis is not difficult if there is a history of rabies or smallpox vaccination or of measles. In cases without such a history, distinction from viral encephalitis may be difficult and at times not possible. Reye's syndrome may be difficult to distinguish from acute disseminated encephalomyelitis. Vomiting at onset, a normal CSF, hyperammonemia, and raised intracranial pressure should suggest Reye's syndrome; frequent convulsions and focal signs argue against it. A distinction from acute MS may not be possible.

PREVENTION AND TREATMENT Since smallpox has been eradicated, there is no longer reason to vaccinate against it. Use of duck embryo and human diploid vaccine in rabies prophylaxis has almost eliminated neuroparalytic accidents, and measles vaccination has drastically reduced what used to be the largest group of postinfectious encephalomyelitides.

Administration of high doses of glucocorticoids every 4 to 6 h is the treatment of choice though controlled trials have not been carried out.

ACUTE NECROTIZING HEMORRHAGIC ENCEPHALOMYELITIS

Acute necrotizing hemorrhagic encephalomyelitis is a rare tissue-destructive disease of the CNS which occurs with explosive suddenness within a few days of an upper respiratory infection. The pathologic findings are distinctive. On sectioning the brain, much of the white matter of one or both hemispheres is seen to be destroyed almost to the point of liquefaction. The involved tissue is pink or yellowish-gray and flecked with multiple small hemorrhages. Sometimes similar

changes are localized to the brainstem or spinal cord. On histologic examination the core lesion resembles that of acute disseminated encephalomyelitis in showing perivenular foci of demyelination, all of like age. As in acute disseminated encephalomyelitis lymphocytes and macrophages are present in the regions of myelin loss, but superimposed on and dominating the picture is an intense polymorphonuclear infiltrate, in keeping with the necrotizing nature of the process. The vessels themselves are partially necrotic; they may contain platelet or fibrin thrombi within their lumens and fibrin deposits beyond their walls. Multiple small hemorrhages at sites of vessel damage are an invariable feature as is a violent inflammatory reaction in the meninges. Large necrotic foci form by coalescence of smaller lesions in the hemispheres, brainstem, or spinal cord.

The clinical course of the illness resembles that of acute disseminated encephalomyelitis save for its apoplectiform onset and rapidity of progress, sometimes leading to death within 48 h. Neurologic signs are frequently unilateral, reflecting disease in one cerebral hemisphere, but may be bilateral. It is probable that certain patients showing an explosive myelitic illness are suffering from a necrotizing myelitis of similar type, but pathologic evidence in support of this view has been difficult to obtain. The CSF examination discloses a more intense reaction than in other demyelinating diseases. Often a polymorphonuclear pleocytosis of up to 2000 cells and a considerable increase in amount of protein are detected. In cases of slower evolution the cell counts are lower and cells are mainly of the mononuclear type.

The etiology of this disease is not established; however, the entire clinical-pathologic entity bears a close resemblance to a hyperacute form of EAE that can be induced in animals by administration of endotoxin, pertussis vaccine, or the vaccine's histamine-sensitizing factor coincident with or shortly after injection of myelin in adjuvant. The lesions in this experimental disease can perhaps be considered as those of a Sanarelli-Shwartzman reaction within the brain superimposed on an acutely demyelinating process. Rarely a lesion like acute necrotizing hemorrhagic encephalomyelitis occurs in MS.

The differential diagnosis of this disorder includes acute encephalitis, particularly those types causing tissue necrosis (herpes simplex, arboviros), acute bacterial cerebritis, septic embolic occlusion of an artery, thrombophlebitis, and suppurative brain abscess. The similarity of acute necrotizing hemorrhagic encephalomyelitis to acute disseminated encephalomyelitis suggests that steroid therapy may be beneficial.

HTLV-I–ASSOCIATED MYELOPATHY (HAM)—TROPICAL SPASTIC PARAPARESIS (TSP)

HAM-TSP presents as a syndrome of progressive spasticity of the lower limbs associated with variable amounts of low back pain, bowel and bladder dysfunction, and disrupted superficial and proprioceptive sensations. The illness develops on a background of HTLV-I infection.

PATHOLOGY The characteristic features are a chronic inflammatory response within the gray and white matter and the meninges; demyelination with relative axonal sparing; proliferation of small blood vessels with perivascular cuffing, and reactive astrocytosis; the above are more marked in the lateral columns of the spinal cord than in the spinothalamic and spinocerebellar tracts. In severe cases, focal spongiosus of tissue is found. Pathologic changes can extend into the brainstem, cerebellum, and cerebrum.

ETIOLOGY Evidence that HTLV-I is the cause of this syndrome includes presence of serum and CSF anti-HTLV-I antibodies, isolation of HTLV-I from systemic and CSF white blood cells; and detection of viral particles within the CNS by electron microscopy. The fact that the immune response is activated coupled with the apparent response of HAM cases to glucocorticoid therapy argues for an immune component in the pathogenesis of tissue injury.

EPIDEMIOLOGY HAM describes the progressive myelopathy syndrome endemic to southern Japan, a temperate climate zone; TSP describes the same etiologic syndrome occurring in tropical regions of the Caribbean, South America, and Africa, affecting mainly, but not exclusively, individuals of black ethnic origin. Peak age of onset of clinical symptoms ranges from 30 to 60 years; childhood onset cases are rare but have been reported from Japan. Females are affected more frequently than males. In endemic areas, prevalence of serum HTLV-I antibodies in the population range from 5 to 20 percent, far exceeding the number of symptomatic individuals. Routes of disease transmission include sexual transmission from male to female, maternal-fetal passage, and blood transfusion. The latency period ranges from 2 years in transfusion cases to many years in maternal-fetal cases. Association of the neurologic syndrome with HTLV-I–induced adult T-cell leukemia is rare. HTLV-I–associated neurologic syndromes have begun to be reported in nonendemic areas.

GENETICS In Japan, specific HLA-region haplotypes are associated with development of the neurologic syndrome; other haplotypes are associated with leukemia.

CLINICAL FEATURES Initial symptoms are usually those of leg weakness with or without back pain. Less frequent complaints are leg paresthesias and bladder dysfunction. Clinical findings include spastic lower limbs with hyperreflexia and Babinski reflexes. In 10 to 60 percent of cases posterior column sensations (proprioception, vibration) are impaired, as are superficial sensations, sometimes with a sensory level that is less well defined than in spinal cord compression syndromes. Less frequent signs include upper limb weakness and spasticity, cerebellar dysfunction, and cranial nerve palsies.

CLINICAL COURSE The progressive myelopathy typically evolves over many years; cases with a more rapid evolution and cases with apparent arrest are also observed.

DIFFERENTIAL DIAGNOSIS Within endemic areas, other causes of myelopathy must be included. Epidemics of "TSP" are on record; such cases are often associated with optic neuropathy and deafness and may be attributable to toxin exposures, particularly with cyanide-containing cassava, malnutrition, or other infectious agents endemic to specific regions, such as treponema. The syndrome of tropical ataxic neuropathy (TAN), characterized by sensory ataxia and slowed peripheral nerve conduction velocities, is also induced by chronic cyanide intoxication (cassava) combined with dietary deficiency. Cases of MS within the endemic TSP-HAM regions do not demonstrate serologic evidence of HTLV-I infection. The severe HTLV-I cases associated with spongiosus of spinal cord need be distinguished from HIV-associated vacuolar myelopathy.

LABORATORY TESTS Within the peripheral blood, T-cell ratios are usually normal, although occasional patients show inverted CD4/CD8 ratios. An increased proportion of T cells express activation antigens compared to controls. Some patients, particularly Japanese, have mild cellular responses within the CSF (up to 50 to 100 cells); in such cases, occasional leukemia-like cells may be found. CSF protein is modestly increased in about 50 percent of cases. Increased CSF immunoglobulin with oligoclonal banding is characteristic. In more than 80 percent of suspected cases, HTLV-I antibodies are detectable in serum and CSF. Virus can be isolated from peripheral blood and CSF. Cerebral lesions are observed on MRI in a minority of cases.

THERAPY Beneficial response to glucocorticoid therapy is claimed in HAM cases; response is less in TSP cases. Viral-directed therapies are under study.

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